Proteomic Insights into Wolbachia-ZIKV Interference in Aedes aegypti

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Zika virus (ZIKV) is a vector-borne disease transmitted primarily by Aedes aegypti mosquitoes. It is associated with severe health outcomes, including microcephaly in newborns and neurological complications such as Guillain-Barré syndrome in adults. To combat ZIKV transmission, one promising approach involves releasing Ae. aegypti mosquitoes infected with Wolbachia pipientis, a maternally inherited endosymbiont that reduces the mosquitoes\' susceptibility to arboviruses and affects their reproductive traits. Despite its potential, the mechanisms by which Wolbachia influences mosquito metabolic pathways, particularly those affecting egg production, remain poorly understood.

In this study, we utilized isobaric labeling-based quantitative proteomics to analyze the impact of Wolbachia wMel and ZIKV coinfections on the proteome of Ae. aegypti ovaries and heads. This approach allowed us to identify a comprehensive proteome, with 3913 proteins detected, including 1044 Wolbachia proteins. Among the 480 modulated mosquito proteins, we observed significant alterations in pathways related to immune response and reproduction.

Our findings revealed that Wolbachia infection enhances immune priming in Ae. aegypti, which likely contributes to the reduced susceptibility to arboviruses. Specifically, Wolbachia modulates the Juvenile Hormone pathway, impacting mosquito fecundity and fertility. Additionally, ZIKV infection was found to disrupt the host immune response by reducing the production of antimicrobial peptides, thereby unsettling the mosquito\'s defense mechanisms.

Coinfection with Wolbachia and ZIKV triggered oxidative stress and resulted in a lack of vitellogenin precursors, essential for egg production. This indicates that both infections can severely impact mosquito reproductive capabilities. Furthermore, our study demonstrated that Wolbachia regulates proteins involved in reactive oxygen species (ROS) production and antioxidant responses, which are crucial for managing cellular stress during infections.

The reduction of ZIKV polyprotein in the presence of Wolbachia, as determined by mass spectrometry, supports the hypothesis that Wolbachia helps block ZIKV infections in Ae. aegypti. This comprehensive proteomic analysis provides valuable insights into the molecular mechanisms underlying Wolbachia-mediated resistance to ZIKV and offers a rich resource of data that can aid in developing new targeted strategies for controlling arbovirus transmission.

To the best of our knowledge, this study represents the most complete proteome analysis of Ae. aegypti ovaries to date. The results highlight the complex interplay between Wolbachia and ZIKV in mosquito hosts and underscore the potential of proteomics to unravel the molecular underpinnings of pathogen interference. By enhancing our understanding of these interactions, we can improve the effectiveness of biocontrol strategies aimed at reducing the burden of ZIKV and other arboviruses.

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